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(54) Title: MICROEMULSIONS COMPRISING THERAPEUTIC PEPTIDES

(57) Abstract

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Pharmaceutical compositions in the form of microemulsions comprise an oil, a mixture of high and low HLB surfactants in which the oil is a propylene glycol or polyol ester of medium chain fatty acids, and high HLB surfactant comprises a medium-chain alkyl/dialkyl sulfate, sulfonate or sulfosuccinate salt dissolved in a polyhydric alcohol, an aqueous phase and optionally further comprises a biologically active agent.

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Microemulsions Comprising Therapeutic Peptides.

Field of the Invention

This invention relates to pharmaceutically acceptable water-in-oil (w/o) self-emulsifying microemulsions containing therapeutic agents, processes for their preparation and their use.

Background of the Invention

Microemulsions can be defined in general as thermodynamically stable, isotropically clear dispersions of two immiscible liquids stabilized by interfacial films of surface-active molecules. The formation of microemulsions usually involves a combination of three to five components, namely, an oil, water, a surfactant, a cosurfactant and an electrolyte. The tendency towards a water-in-oil (w/o) or an oil-in-water (o/w) microemulsion is dependent on the properties of the oil and the surfactant. Surfactants are conveniently classified on an empirical scale known as the hydrophilic-lipophilic balance (HLB) which runs from 1 to 45. In general, (w/o) microemulsions are formed using surfactants (or emulsifiers) which have an HLB value in the range of about 3 to 6 while (o/w) microemulsions are formed using surfactants which have an HLB value in the range of about 8 to 18. It has long been recognized that low interfacial tension contributes to the thermodynamic stability of microemulsions. To achieve this, the surfactant should preferably exhibit low solubility in both the oil and water phases, and be preferentially absorbed at the water-oil interface with concomitant lowering of interfacial tension. When interfacial tension is less than 2×10^{-2} dyn/cm, a stable microemulsion can form. General reviews of microemulsions are provided by Bhargava *et al.*, Pharm. Tech., 46-53, March 1987 and Kahlweit, Science, 240, 617-621, 1988.

Microemulsions are typically substantially non-opaque, i.e. are transparent or opalescent when viewed by optical microscopic means. In the undisturbed state, they are optically isotropic (non-birefringent) when examined under polarized light. The dispersed phase typically comprises particles or droplets which are normally between 5 and 200 nm in size and this gives rise to their optical transparency. These particles may be spherical although other structures are feasible.

The role of the cosurfactant, usually a short-chain alcohol, is to increase the interfacial fluidity by penetrating the surfactant film and consequently creating a disordered film due to the void space among surfactant molecules. The use of a cosurfactant in microemulsions is however optional and alcohol-free self-emulsifying emulsions and

microemulsions have been described in the literature (see for instance, Pouton et al., Int. Journal of Pharmaceutics, 27, 335-348, 1985 and Osborne *et al.*, J. Disp. Sci. Tech., 9, 415-423, 1988).

There are many advantages to the use of a microemulsion over a conventional emulsion (or macroemulsion) for drug transport (delivery). Microemulsions form spontaneously, without the need for a high input of energy and are therefore easy to prepare and scale up for commercial applications; they have thermodynamic stability due to their small particle size and therefore have a long shelf life; they have an isotropically clear appearance so that they may be monitored by spectroscopic means; they have a relatively low viscosity and are therefore easy to transport and mix; they have a large interfacial area which accelerates surface reactions; they have a low interfacial tension which permits flexible and high penetrating power and, lastly, they offer the possibility of improved drug solubilization and protection against enzymatic hydrolysis. In addition, microemulsions may undergo phase inversion upon addition of an excess of the dispersed phase or in response to a temperature change and this is a property of these systems that can affect drug release from microemulsions both *in vitro* and *in vivo*. The reasons for this improved drug delivery are not however well understood.

Lipid-based microemulsions have already been proposed to enhance the bioavailability of different drugs, including peptides. Thus, GB 2 222 770-A (Sandoz Ltd) describes microemulsions and corresponding microemulsion "pre-concentrates" for use with the highly hydrophobic cyclosporin peptides. Thus, a suitable pre-concentrate comprises 1,2-propylene glycol as the hydrophilic component, a caprylic-capric acid triglyceride as the lipophilic component and a mixture of a polyoxyethylene glycolated hydrogenated castor oil and glycerin monooleate (ratio 11:1) as the surfactant-cosurfactant. Such formulations may then be diluted with water but to give an oil-in-water rather than a water-in-oil microemulsion.

In addition, GB 2 098 865A (Sandoz Ltd) describes topical compositions in the form of microemulsions comprising a water-immiscible organic solvent, an emulsifier, a co-emulsifier, water and a (non-peptide) therapeutic agent. These formulations are said to have improved skin penetrating properties. Suitable organic solvents include (C_{10-22})-fatty acid esters of (C_{3-18})-alcohols such as hexyl laurate, (C_{12-32})-hydrocarbons such as squalene and mono- or diesters of glycerol with a (C_{6-22}) carboxylic acid such as glyceryl caprylate (which may also act as a co-emulsifier). There is however no mention of using a medium-chain fatty acid triglyceride as the oil.

Furthermore, US 4 712 239 (Muller *et al.*) describes multi-component systems for pharmaceutical use comprising an oil, a nonionic surfactant with an HLB value above 8 and a co-surfactant which is a partial ether or ester of a polyhydroxyl alcohol and a (C_{6-22}) fatty alcohol or acid, which components form a "single phase" on mixing. The special properties of the system are attributed to the particular blend of surfactant and co-surfactant selected. An aqueous phase is an optional extra and the therapeutic agent may be lipophilic or hydrophilic. Such systems are said to give enhanced transdermal delivery characteristics. Amongst the examples provided, one (example 1, formulation I) has PEG 20 Ethylene oxide (20 EO)-oleic acid glycerol partial esters (40%), caprylic-capric acid glycerol partial esters (42% monoglyceride content, 24%), medium-chain triglycerides (16%) and water (20%). It is to be noted that the ratio of the medium-chain triglyceride to the caprylic-capric acid glycerol partial esters is 1:1.5. In comparison example 1, this is formulated with the drug arecaidine *n*-propyl ester HCl salt. A further example (example 1, formulation VII) incorporates a macromolecule, the polypeptide hirudin but in this, the oil is *iso*-propyl palmitate.

Finally, WO 88/00059 (Engström *et al.*, and the corresponding paper, J. Dispersion Sci. Technol., 11, 479, 1990) discloses controlled release compositions for biologically active materials comprising an "L2-phase" and containing an unsaturated (C_{16-22})-fatty acid monoglyceride and an unsaturated (C_{16-22})-fatty acid triglyceride, in a ratio of from 1:1 to 3:1, and a polar liquid such as water. Such an unsaturated (C_{16-22})-fatty acid monoglyceride is a low HLB surfactant and there is no mention of the additional inclusion of a high HLB surfactant. In addition, a long-chain rather than a medium-chain derivative is used. The existence of an L2 phase had previously been described for a water/monocaprylin/tricaprylin system by Friberg *et al.*, J. Amer. Oil Chem. Soc., 47, 149, 1970. Again, there is no mention of the additional inclusion of a high HLB surfactant.

Dioctyl sodium sulfosuccinate (DSS) better known as Docusate Sodium or Aerosol OT is widely used as a solubilizing, wetting, emulsifying or dispersing agent. Known pharmaceutical uses of DSS include: a) as a therapeutic agent, alone or as an adjuvant in the prevention or treatment of constipation, b) as a tablet formulation adjuvant to facilitate tablet coating and improve tablet disintegration and dissolution characteristics, and c) as an absorption enhancer. DSS has been reported to increase the small intestinal absorption of heparin (Engel, R.H. et al.; J. Pharm. Sci. 58, 706-710, 1969), insulin (Dupont, A. et al.; Ugeskrift Lager 119, 1461-1463, 1957) and phenolsulfonphthalein (Khalaffalah, N. et al.; J. Pharm. Sci. 64, 991-994, 1975).

Microemulsions as topical drug delivery vehicles formed by the system water/octanol/dioctyl sulfosuccinate have been reported by Osborne, D.W. et al.; (Drug Dev. Ind. Pharm. 14, 1203-1219, 1988; J. Pharm. Pharmacol. 43, 451-454, 1991). These studies have shown that in vitro transdermal flux of hydrophilic drugs is highly dependent upon the composition of microemulsion, particularly on the octanol/DSS ratio. In vitro release of lipophilic drugs from oil-in-water microemulsions consisting of isopropyl myristate (oil), 1-butanol, (co-surfactant), dioctyl sodium sulfosuccinate and water/buffer have been described by Trotta, M. et al.; (J. Control. Rel. 10, 237-243, 1989; Acta Pharm. Technol. 36, 226-231, 1990).

EP-387647 (Matouschek, R.) describes pharmaceutical microemulsion compositions containing acidic or basic drug and compound forming ion-pairs for nasal, rectal or transdermal delivery. Suitable oils included isopropyl myristate, 2-octyl dodecanol and paraffin oil with the surfactant comprising polyoxyethylene fatty acid ester and/or polyoxyethylene fatty alcohol ether. The cosurfactant used was polyoxyethylene glycerol fatty acid ester with water being the aqueous phase. In the case of basic drugs the compound forming an ion-pair was sulphate.

Pharmaceutical microemulsion compositions which have improved solubility, stability and/or particle size for the oral delivery of therapeutic agents, in particular for peptides, is still needed.

Summary of the Invention

Improved drug delivery characteristics may be obtained using microemulsions having a lipophilic phase having certain relative amounts of medium-chain fatty acid propylene glycol and/or polyol esters and low HLB surfactant, in combination with a high HLB surfactant and an aqueous-based hydrophilic phase.

Accordingly, the present invention provides a pharmaceutically acceptable, stable, self-emulsifying microemulsion comprising:

(a) a lipophilic phase comprising medium-chain fatty acid propylene glycol and/or polyol esters and a low HLB surfactant, in which the ratio of the medium-chain fatty acid propylene glycol and/or polyol esters to the low HLB surfactant is from 5:1 to 1.5:1;

(b) an admixture of a polyol and at least one high HLB surfactant which is

i) a sulfate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfate, an aryl sulfate, an aliphatic-aryl sulfate, or mixtures thereof;

ii) a sulfonate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfonate, or aryl sulfonate, an aliphatic-aryl sulfonate, or mixtures thereof;

iii) a sulfosuccinate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfosuccinate, an aryl sulfosuccinate, an aliphatic-aryl sulfosuccinate, or mixtures thereof; or

iv) a mixture of any of i), and/or ii), and/or iii) above;

(c) an aqueous hydrophilic phase; and

(d) a water-soluble therapeutic agent.

Brief Description of the Drawings

The accompanying drawings contain the following figures:

Figure 1 illustrates a pseudo-ternary phase diagram reading of a microemulsion system containing an oil and a low HLB surfactant in a fixed ratio X, a high HLB surfactant and an aqueous phase.

Figure 2 illustrates a pseudo-ternary phase diagram of the microemulsion system CAPTEX 200/CAPMUL C8 as the oil/low HLB surfactant in a ratio of 2 to 1, labelled as component (1); DSS/PEG 400 (1:1) as the high HLB surfactant, labeled as component (3); and water as the aqueous phase, labeled as component (2).

Detailed Description of the Invention

The microemulsions of the present invention without a biologically therapeutic drug are novel and useful as precursors to drug-containing microemulsions. Accordingly, the present invention provides for a stable, self-emulsifying water-in-oil (w/o) or oil-in-water (o/w) microemulsion comprising:

(a) a lipophilic phase comprising a medium-chain fatty acid propylene glycol ester and/or a medium-chain fatty acid polyol esters, or mixtures thereof, and a low HLB surfactant; in which the ratio of the medium-chain fatty acid propylene glycol and/or polyol esters to the low HLB surfactant is from 5:1 to 1.5:1;

(b) an admixture of a polyol and at least one high HLB surfactant which is

i) a sulfate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfate, an aryl sulfate, an aliphatic-aryl sulfate, or mixtures thereof;

ii) a sulfonate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfonate, or aryl sulfonate, an aliphatic-aryl sulfonate, or mixtures thereof;

iii) a sulfosuccinate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfosuccinate, an aryl sulfosuccinate, an aliphatic-aryl sulfosuccinate, or mixtures thereof; or

iv) a mixture of any of i), and/or ii), and/or iii) above;

(c) an aqueous hydrophilic phase in which each of (a), (b) and (c) are as hereinbelow defined and pharmaceutically acceptable.

In a further aspect the present invention provides for a pharmaceutically acceptable, stable, self-emulsifying microemulsion comprising each of (a), (b) and (c) above and (d) a water-soluble therapeutic agent.

The inclusion in a microemulsion of an aliphatic, preferably a medium chain alkyl or dialkyl, sulfate or sulfonates or sulfosuccinate is believed to enhance the absorption of a biologically active agent when administered in the above formulations, particularly in reference to field A in Figure 2.

Suitable medium-chain fatty acid propylene glycol and/or polyol esters for use in the present invention may be of natural, semi-synthetic or synthetic origin and may include blends of different medium chain fatty acid esters, and/or medium and long chain fatty acid esters. Such blends include not only physical blends of medium- and long-chain fatty acid esters but also esters which have been chemically modified, by for instance, interesterification, to include a mixture of medium- and long-chain fatty acyl moieties. Suitable esters are readily available from commercial suppliers.

For preferred medium-chain fatty acyl esters, the fatty acid composition comprises caprylic (C_8) acid optionally admixed with capric (C_{10}) acid, for instance from 50 to 100% (w/w) of caprylic acid and from 0 to 50% (w/w) of capric acid esters.

Prefered lipophilic phase medium chain esters for use herein include those which are either propylene glycol based or polyethylene based. Such examples include those available under the trade names MYRITOL; CAPTEX (Karlshams Lipid Specialties, Columbus OH), for instance CAPTEX 200; MIGLYOL (BASF), for instance the grades MIGLYOL 840; SOFITIGEN (Huls America Inc., Piscataway NJ), for instance SOFTIGEN 767; LABRAFAC and LABRASOL (Gattefosse Corp., Westwood, NJ), for instance LABRAFAC CM-10. Propylene glycol examples are CAPTEX 200 and Miglyol 840 are propylene glycol dicaprylate/dicaprate systems. PEG based systems are Softigen 767, which is a PEG-6 Caprylic/Capric Glyceride system; LABRAFAC CM-10 are the glycerol and PEG esters of C_8 and C_{10} fatty acids, and LABRASOL is a PEG-8 Caprylate/Caprate glyceride ester system.

As used herein, the term "polyol" as in "polyol ester" in the lipophilic phase is a compound which contains one or more ester linkages derived from a polyhydric alcohol, i.e. a carbon backbone containing two or more hydroxyl groups. Such carbon backbones for making such esters include but not limited to, ethylene glycol, propylene glycol or polyethylene glycol (PEG). PEG is also referred to as a polyglycol with ethylene glycol

as a polymerized unit. Preferably, the polyol is propylene glycol or a polyethylene glycol.

The term "medium-chain" such as in "medium-chain fatty acid", and as used herein refers to a carbon chain, which may be saturated, mono-unsaturated or poly-unsaturated, having from 6 to 12, preferably from 8 to 10 carbon atoms, which may be branched or unbranched, preferably unbranched, and which chain may be optionally substituted. Optional substituents include for instance, halogen, hydroxy, alkoxy, thioalkyl or halo substituted alkyl. Halogen, as used herein includes F, Cl, Br and I.

The term "long-chain" such as in "long-chain fatty acid", and as used herein refers to a carbon chain,which may be saturated, mono-unsaturated or poly-unsaturated, having from 14 to 22, preferably 14 to 18, carbon atoms which may be branched or unbranched, preferably unbranched, and which may be optionally substituted as noted above for medium chain fatty acids.

In microemulsions of the present invention a non-ionic high HLB surfactant may be usefully included as an auxiliary high HLB surfactant. Suitably, the non-ionic high HLB surfactant has an HLB in the range of 15 to 45. Suitably, the ratio of the aliphatic or aryl or aliphatic-aryl sulfate or sulfonate or sulfosuccinate to the non-ionic high HLB surfactant is at from 10:1 to 1:1. Preferably from 10:1 to 3:1 and most preferably about 10:1.

Suitable low HLB surfactants for use in the present invention include fatty acyl monoglycerides, fatty acyl diglycerides, sorbitan medium or long-chain fatty acyl esters and medium-chain free fatty acids, as well as mixtures thereof. Suitable mono- and di-glycerides may each include blends of different fatty acyl mono- and di-glycerides and the fatty acid moieties may be medium- or long-chain or a mixture thereof.

Suitable medium chain fatty acyl mono- and di-glycerides are formed from caprylic and capric acids. Suitable blends comprise from about 50 to 100% caprylic acid and from 0 to 50% capric acid. Mixtures of mono-and di-glycerides preferably comprise at least 50, more preferably at least 70% by weight of monoglycerides. Suitable commercial sources of these include the products available under the trade name CAPMUL (Karlsham Lipid Specialties), for instance the products CAPMUL MCM which comprises monoglycerides (77%), diglycerides (21%) and free glycerol (1.6%), with a fatty acid composition which comprises caproic acid (3%), caprylic acid (67%) and capric acid (30%) and CAPMUL C_8 which has monoglycerides (70 - 90%), diglycerides (10 - 30%) and free glycerol (2 - 4%), with a fatty acid composition which comprises at least 98% caprylic acid

(manufacturer's data expressed as oleates; actual C8/10 mono- and diglyceride content of about 45%, respectively).

In a preferred embodiment of the present invention, the low HLB surfactant contains a mixture of mono- and diglycerides having at least about 80% by weight, preferably at least about 90% by weight, and more preferably at least about 95% by weight of a caproic, caprylic, capric monoglyceride or mixtures thereof, preferably a caproic, caprylic, capric monoglyceride or mixtures thereof, more preferably a caprylic, capric monoglyceride or mixtures thereof. Commercial examples of these surfactants include IMWITOR 308 (Huls America, Inc.) which has about 80-90% wt. caprylic monoglycerides; and Glycerol Monocaprylin, manufactured as 1-monoctanoyl-rac-glycerol (Sigma Chemicals) having about 99% wt. caprylic monoglycerides; and Glycerol Monocaprate, manufactured as 1-monodecanoyl-rac-glycerol (Sigma Chemicals) having about 99% wt. capric monoglycerides.

Suitable long-chain fatty acyl monoglycerides include glycerol monooleate, glycerol monopalmitate and glycerol monostearate. Suitable commercially available examples of such include the products available under the trade names MYVEROL, such as MYVEROL 18-92 (a sunflower oil monoglyceride) and18-99 (a rapeseed oil monoglyceride), MYVATEX and MYVAPLEX, respectively, from Eastman Kodak Chemicals, Rochester, New York. A further useful long-chain fatty acyl monoglyceride-containing product is ARLACEL 186 (available from ICI Americas Inc.) which includes, in addition to glycerol monooleate, propylene glycol (10%). The main fatty acids of MYVEROL 18-92 are oleic acid (19%), linoleic acid (68%) and palmitic acid (7%) while those of MYVEROL 18-99 are oleic acid (61%), linoleic acid (21%), linolenic acid (9%) and palmitic acid (4%). Suitably in such long-chain monoglycerides, the major fatty acid component is a C_{18}-saturated, monounsaturated or polyunsaturated fatty acid, preferably a C_{18}-monounsaturated or polyunsaturated fatty acid. In addition, diacetylated and disuccinylated versions of the monoglycerides such as the product available under the trade name MYVATEX SMG are also useful.

Suitable sorbitan long-chain esters for use in the present invention include sorbitan monooleate, available commercially under the trade names SPAN 80 and ARLACEL 80 and sorbitan sesquioleate, available commercially under the trade names SPAN 83 and ARLACEL 83. Suitable sorbitan medium-chain esters for use in the present invention include sorbitan caprylate, sorbitan caprate, sorbitan laurate.

Suitable medium-chain fatty acids for use in the present invention include caprylic and capric acids and mixtures thereof.

Suitably the low HLB surfactant will have an HLB value in the range of about 2 to 8. The HLB values of the products CAPMUL MCM, MYVEROL 18-99, ARLACEL 80, ARLACEL 83 and ARLACEL 186 are respectively about 5.5 to 6, 3.7, 4.3, 3.7 and 2.8. The estimated HLB of 1-monocaprylin is about 8.0.

In a preferred embodiment of the present invention, microemulsions comprise medium-chain fatty acyl components, such as those derived from caprylic and capric acids, especially those derived from caprylic acid. Accordingly, preferred microemulsions include blends of CAPTEX 200, Miglyol 840, Softigen 767, Labrafac CM-10, and Labrasol , and particularly CAPTEX 200, with CAPMUL MCM or CAPMUL C_8, particularly CAPMUL C_8.

The use in a self-emulsifying (w/o) microemulsion according to the present invention of a low HLB surfactant which is a medium-chain fatty acid monoglyceride and/or a medium-chain fatty acid diglyceride as hereinbefore defined and which is a component of the lipophilic phase provides for reduced droplet size and together with the high HLB surfactant this is believed to aid in the absorption of the therapeutic agent.

Accordingly in a preferred aspect the present invention provides for a microemulsion in which the medium-chain fatty acid propylene glycol and/or polyol ester is a caprylic acid or a blend of caprylic and capric acids esters as hereinbefore defined and in which the low HLB surfactant is a medium-chain fatty acid monoglyceride or diglyceride or a mixture thereof in which the medium-chain fatty acid is caprylic acid or a mixture of caprylic and capric acids as hereinbefore defined, optionally admixed with a small amount of medium-chain fatty acid, in particular, a blend of caprylic acid triglyceride and caprylic acid monoglyceride or diglyceride or mixture thereof.

The high HLB surfactant for use in the present invention is an aliphatic, aryl or an aliphatic-aryl sulfate, sulfonate or sulfosuccinate. The aliphatic moiety is a medium or long chain alkyl or dialkyl group. The medium chain moiety contains C_6 to 12, preferably 8 to 10 carbons, and the long chain moiety contains from C_{12} to 24 , preferably 14 to 18 carbons as previously defined. The aliphatic chain may be branched or unbranched, may be optionally substituted, and may be saturated, mono-unsaturated or poly-unsaturated. Preferably the aliphatic moiety is of medium chain length.

There are two contemplated forms of linkages possible with the sulfate, sulfonate and sulfosuccinate groups for use herein. One is designated as a fatty acyl ester linkage and the other an ester linkage. If the aliphatic or aryl moiety forms an fatty acyl ester linkage

with the sulfate, sulfonate or sulfosuccinate, i.e. contains an additional carbonyl [C(O)] group, the aliphatic (or aryl) group becomes known as the fatty acid portion of the ester linkage. A fatty acyl ester linkage, is for instance, a C_{6-12}-C (O) - O S(O)3Na+ . This is in contrast to the generally recognized linkage of C_{6-12} C-O - S(O)3Na+, referred to herein as the ester linkage. This terminology stems from the reaction of a C_{6-12} OH moiety with the sulfonic acid O-$S(O)_2$ - Na^+ group forming a sulfonic ester. Preferably the linkage is an ester linkage and not a fatty acyl ester linkage. More preferably the linking group is a medium chain alkyl or dialkyl moiety.

As used herein the term "aryl" sulfate, sulfonate or sulfosuccinate means a phenyl or naphthyl moiety. Suitable aryl sulfonates include, for instance, benzene sulfonate.

As more than one site for attachment is possible with the sulfates, sulfonates and sulfosuccinates another aspect of the invention is the use of mixtures of aliphatic and aryl linkages in the same moiety, such as dodecyl benzene sulfate. This combination as used herein is referred to as "aliphatic-aryl". Preferably the aliphatic moiety in this instance is a medium chain alkyl or dialkyl group.

Suitable long chain alkyl or dialkyl sulfates, sulfonates and sulfosuccinates include, but are not limited to myristic (C14), palmitic (C16), palmitoleic (C16:1), stearic (C18), oleic (C18:1), vaccenic (trans oleic acid) or linoleic (C18:2) . Suitably, the alkyl and dialkyl moieties may be mixtures of different medium and long chain moieties, such as a dialkyl sulfate having a C12 and a C16 group.

Preferably the sulfates, sulfonates and sulfosuccinates are medium chain alkyl or dialkyl derivatives. Suitable medium chain moieties include, but are not limited to octyl (C_8), decyl (C_{10}), dodecyl (C_{12}), iso-octoanoic, or di-octyl, di-decyl, or di-dodecyl. Preferably, the medium chain moiety is octyl, decyl, dodecyl, or dioctyl. More preferably, the high HLB is a octyl, decyl, dodecyl or di-octyl sulfosuccinate, or is a octyl, decyl, or dodecyl sulfate.

Yet another aspect of the instant invention is the combination of mixtures of the different aliphatic, aryl or aliphatic-aryl sulfates, sulfonates and sulfosuccinates as the high HLB surfactant used herein.

Suitably, the sulfates, sulfonates, or sulfosuccinates will be pharmaceutically acceptable water-soluble salts, for instance alkali metal salts, such as sodium and potassium salts, or ammonium or quaternary ammonium salts also referred to as $N(R)_4$ wherein R is an alkyl derivative, or is a primary and secondary (protonated) amine salt, such as ethanolamine

or triethanolamine. Preferably, the salts are the alkali metal salts. Suitably, the salts are salts of the medium chain alkyl or dialkyl sulfates, such as octyl, decyl, dioctyl, or dodecyl sulfate; or the salts of the dialkyl sulfosuccinates such as noted above, of which the salts sodium dioctyl sulfosuccinate and sodium dodecyl sulfate are preferred. Sodium dioctyl sulfosuccinate (DSS) and sodium dodecyl sulfate (SDS) have estimated HLB values of 41 and 40 respectively.

As used herein, the term "polyol" is a polyhydric alcohol, i.e. containing two or more hydroxyl groups. Such as but not limited to, ethylene glycol, propylene glycol or polyethylene glycol (PEG). PEG is also referred to as a polyglycol with ethylene glycol as a polymerized unit. Preferably, the polyol has three or more alcoholic units and is glycerol or a PEG. More preferably, the polyol is a PEG having a molecular weight of 400 (PEG-400). Other suitable polyhydric alcohol's for use herein include, but not limited to, ethylene glycol (2-OH units), sorbitol (6-OH), and mannitol (6-OH).

The ratio of the sulfates, sulfonates, or sulfosuccinates to the polyol is from about 10:1 to 1:1, preferably about 1:1.

Commerically available DSS includes all in USP grades DSS (100%), DSS 85% surfactant (with 15% sodium benzoate) or DSS (50%) in PEG 400 (1:1).

Suitably, the admixture for use herein is a polyol with at least one high HLB surfactant which is a sulfate, or a sulfonate, or a sulfosuccinate or pharmaceutically acceptable salts thereof. The sulfate moiety, or a pharmaceutically acceptable salt thereof, may be an aliphatic sulfate, an aryl sulfate, an aliphatic-aryl sulfate, or a mixture thereof. The sulfonate or pharmaceutically acceptable salt thereof, may be an aliphatic sulfonate, aryl sulfonate, an aliphatic-aryl sulfonate, or a mixture thereof. The sulfosuccinate or pharmaceutically acceptable salt thereof, may be an aliphatic sulfosuccinate, an aryl sulfosuccinate, an aliphatic-aryl sulfosuccinate, or a mixture thereof. The high HLB surfactant may be a mixture of any of the above noted sulfates, sulfonates or sulfosuccinates and their pharmaceutically acceptable salts thereof. Such a mixture could be referred to as binary or ternary mixture of the sulfate groups, the sulfonate groups or sulfosuccinate groups.

The preferred high HLB is a medium chain alkyl or dialkyl sulfate, sulfonate or sulfosuccinate or pharmaceutically acceptable salts thereof.

The total amount of high HLB surfactant which is a sulfate, sulfonate and sulfosuccinate should comprise at least 50% of the total amount by weight of high HLB surfactant

required to be present in the formulation. It is recognized that other high HLB surfactants may be present in the formulation and are further described herein. Suitably, the total amount of high HLB surfactant present should range from about 5 % to about 30% (w/w) and from about 70% to less than 100% (w/w). It is of these amounts that at least 50% (w/w) should be comprised of the sulfate, etc. surfactants. Any additional non-ionic, ionic and zwitterionic surfactants should comprise no more than 50% of the total high HLB surfactant present in the formulation, preferably 10% or less.

Optionally, the high HLB surfactant may contain additional excipients or co-surfactants and include, but are not limited to the

1) non-ionic surfactants, such as

(a) polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type available under the trade name MYRJ (ICI Americas, Inc.), for instance the product MYRJ 52 (a polyoxyethylene 40 stearate);

(b) polyoxyetheylene-sorbitan fatty acid esters (polysorbates), for example the mono- and tri-lauryl, palmityl, stearyl and oleyl esters, for instance the polyoxyethylene sorbitan monooleates available under the trade name of TWEEN (ICI Americas Inc.), such as TWEEN 20, 21, 40, 60, 61, 65, 80, 81 and 85, of which class TWEEN 80 is especially preferred;

(c) PEG glycerol ethers, such as the polyethylene glycol long-chain alkyl ethers, which include polyethylated glycol lauryl ether; and PEG fatty alcohol ethers; and

(d) PEG glycerol esters and PEG fatty acid esters, such as the long-chain alkyl esters, which include PEG-monostearate;

The surfactant system may contain additional surfactants and include, but not limted to:
1) cationic surfactants, such as cetyl ammonium bromide (CTAB) or benzalkonium bromide;

2) anionic surfactants, such as bile salts and the alkali metal salts thereof, including but not limited to cholate, deoxycholate, taurocholate, etc., sodium taurocholate and C_{6-18} fatty acyl carnitines; or

3) low HLB surfactants, such as other lipids, i.e., phospholipids which may be anionic, cationic or zwitterionic, in particular lecithins, such as soya bean lecithins, egg lecithin or egg phosphatide, cholesterol or long-chain fatty acids such as oleic acid.

As used herein, the term "therapeutic agent" (hereinafter referred to as "drug") refers to any compound which has biological activity, is soluble in the hydrophilic phase and has an HLB value of at least that of the high HLB surfactant used in the formulation, to

ensure that the drug is preferentially dissolved in the hydrophilic rather than the lipophilic phase. This includes both peptides and non-peptides. Suitable peptides include not only small peptides but also larger peptides/polypeptides and proteins. Suitable such peptides preferrably have a molecular weight from about 100 to 10,000, more preferably from about 100 to about 6,000. Especially preferred are peptides having from 2 to 35 amino acid moieties. Higher molecular weight peptides, even those with a molecular weight of above 10,000, up to about 50,000, may also be accomodated in microemulsions of the present invention.

Suitable small peptides have from about 2 to about 10, more preferably from about 2 to about 6 amino acid moieties. Preferred small peptides include the fibrinogen receptor antagonists (RGD containing peptides) which are tetrapeptides with an average molecular weight of about 600. These peptide antagonists are highly potent platelet aggregation inhibitors at plasma levels as low as 1 pmol/ml. Preferred fibrinogen antagonists include the peptide cyclo(S,S)-N^a-acetyl-Cys-(N^a-methyl)Arg-Gly-Asp-Pen-NH_2 (Ali *et al.*, EP 0 341 915, whose disclosure is herein incorporated by reference in its entirety) and the peptide cyclo(S,S)-(2-mercapto)benzoyl-(N^a-methyl)Arg-Gly-Asp-(2-mercapto)phenylamide (EP 0 423 212, whose disclosure is herein incorporated by reference in its entirety). Other fibrinogen antagonists useful in the present invention are those peptides disclosed by Pierschbacher *et al.*, WO 89/05150 (US/88/04403); Marguerie, EP 0 275 748; Adams *et al.*, U.S. 4,857,508; Zimmerman *et al.*, U.S. 4,683,291; Nutt *et al.*, EP 0 410 537, EP 0 410 539, EP 0 410 540, EP 0 410 541, EP 0 410 767, EP 0 410 833, EP 0 422 937 and EP 0 422 938; Ali *et al.*, EP 0 372 486; Ohba *et al.*, WO 90/02751 (PCT/JP89/00926); Klein *et al.*, U.S. 4,952,562; Scarborough *et al.*, WO 90/15620 (PCT/US90/03417); Ali *et al.*, PCT/US90/06514 and PCT/US92/00999; the peptide-like compounds disclosed by Ali *et al.*, EP 0 381 033 and EP 0 384 362; and the RGD peptide cyclo-N^a-acetyl-Cys-Asn-Dtc-Amf-Gly-Asp-Cys-OH (in which Dtc is 4,4'-dimethylthiazolidine-5-carboxylic acid and Amf is 4-aminomethylphenylalanine).

The RGD peptide may be usefully included in the microemulsion formulation in an amount up to about 600mg/g of the hydrophilic phase or from 0.1 to 60 mg/g of the formulation.

Other peptides useful in the present invention include, but are not limited to, other RGD containing peptides such as those disclosed by Momany, U.S. 4,411,890 and U.S. 4,410,513; Bowers *et al.*, U.S. 4,880,778, U.S. 4,880,777, U.S. 4,839,344; and WO 89/10933 (PCT/US89/01829); the peptide Ala-His-D-Nal-Ala-Trp-D-Phe-Lys-NH_2 (in which Nal represents ß-naphthylalanine) and the peptides disclosed by Momany, U.S.

4,228,158, U.S. 4,228,157, U.S. 4,228,156, U.S. 4,228,155, U.S. 4,226,857, U.S. 4,224,316, U.S. 4,223,021, U.S. 4,223,020, U.S. 4,223,019 and U.S. 4,410,512.

Other suitable peptides include hexapeptides such as the growth hormone releasing peptide (GHRP) His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2, (Momany, US 4,411,890, the disclosure of which is herein incorporated by reference in its entirety). This may usefully be included in an amount up to about 250mg/g of the hydrophilic phase or from 0.1 to 25mg/kg of the formulation.

Suitable larger polypeptides and proteins for use in microemulsions of the present invention include insulin, calcitonin, elcatonin, calcitonin-gene related peptide and porcine somatostatin as well as analogs and homologs thereof. Other suitable larger polypeptides include those disclosed by Pierschbacher *et al.*, U.S. 4,589,881 (>30 residues); Bittle *et al.*, U.S. 4,544,500 (20-30 residues); and Dimarchi *et al.*, EP 0 204 480 (>34 residues).

Other type of compounds useful in the present invention include analogs or homologs of LHRH which display potent LH releasing activity or inhibit the activity of LHRH; analogs or homologs of HP5 which possesses hematopoetic activity; analogs or homologs of endothelin which possess hypotensive activity; analogs or homologs of enkephalin which have antinociceptive activity; analogs or homologs of chlorecystokinin; analogs or homologs of cyclosporin A which have immunosuppressive activity; analogs or homologs of atrial natriuretic factor; peptidergic antineoplastic agents; analogs or homologs of gastrin releasing peptide; analogs or homologs of somatostatin; gastrin antagonists; bradykinin antagonists; neurotensin antagonists; bombesin antagonists; oxytocin agonists and antagonists; vasopressin agonists and antagonists; hirudin analogs and homologs; analogs and homologs of the cytoprotective peptide-cyclolinopeptide; alpha MSH analogs; analogs, and homologs of MSH releasing factor (Pro-Leu-Gly-NH_2); peptides which inhibit collagenase; peptides which inhibit elastase, peptides which inhibit renin; peptides which inhibit HIV protease; peptides which inhibit angiotensin converting enzyme; peptides which inhibit chymases and tryptases and peptides which inhibit blood coagulation enyzmes.

Other suitable drugs include non-peptide therapeutic agents such as antibotics, antimicrobial agents, antineoplastic agents, cardiovascular and renal agents, antiinflammatory, immunosuppressive and immunostimulatory agents and CNS agents.

Preferably, the drug is a peptide such as a fibrinogen receptor antagonist peptide (an RGD peptide), GHRP (His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2), a vasopressin, a calcitonin or an

insulin, more preferably the fibrinogen receptor antagonist peptides cyclo(S,S)-N^a-acetyl-Cys-(N^a-methyl)Arg-Gly-Asp-Pen-NH_2 or cyclo(S,S)-(2-mercapto)benzoyl-(N^a-methyl)Arg-Gly-Asp-(2-mercapto)phenylamide or GHRP.

In a prefered aspect, the present invention provides microemulsions comprising a peptide which may be orally administered and which will retain biological activity, thereby overcoming the disadvantages of earlier formulations in which the bioavailability of the peptide has been less than satisfactory. In particular, the present invention provides formulations which by their nature permit the preparation and administration of a peptide in sufficiently high concentration to allow not only convenient oral administration but also adequate bioavailability of the peptide.

For a water-soluble drug, the degree of incorporation into the (w/o) microemulsions of the present invention is limited only by its solubility in the hydrophilic phase. By a person skilled in the art, isotonic aqueous phase in the physiological pH range (3 - 8) may be used to aid drug dissolution by the proper modification of the PEG (400) and the high HLB surfactant salt ratio, in particular the medium chain alkyl/ dialkyl, sulfate or sulfonate or sulfosuccinates, without compromising the integrity of the active ingredient and stability of the composition.

The aqueous hydrophilic phase suitably comprises water or an isotonic saline solution and may also include a pharmaceutically acceptable solvent which is non-miscible with the selected lipophilic phase, such as polyethylene glycol, propylene glycol, sorbitol, mannitol and other mono- or di-saccharides.

It will be readily appreciated by the skilled person that not all blends of a medium-chain fatty acid triglyceride, low and high HLB surfactants and hydrophilic phase will yield stable, self-emulsifying microemulsions within the scope of the present invention. Appropriate ratios may, however, be readily determined by the skilled man with the aid of a phase diagram such as that illustrated in Fig. 1. As the system comprises four components *viz* a medium-chain fatty acid triglyceride (oil), a low HLB surfactant, a high HLB surfactant and an aqueous/hydrophilic phase, a pseudo-ternary phase diagram is employed. In this, the ratio of two components such as the oil and the low HLB surfactant is kept constant so that there are only three variables, each of which can then be represented by one side of the triangle. Thus, in fig. 1, (1) represents the mixture of the oil and the low HLB surfactant, at a fixed ratio X, (2) the hydrophilic (aqueous) phase and (3) the high HLB surfactant. By way of example, the point "A" represents a mixture 50% oil plus low HLB surfactant, 20% aqueous phase and 30% high HLB surfactant.

The regions of the phase diagram in which microemulsions according to the present invention exist may be determined by titrating a mixture of the oil and low HLB surfactant (in a fixed ratio) against the high HLB surfactant and the hydrophilic phase, noting points of phase separation, turbidity and transparency. Clear, transparent formulations are indicative of the formation of a stable microemulsion. Liquid and gel formulations may be obtained at room temperature according to the specific nature of the components employed.

Once stable transparent systems are obtained, simple tests, such as dye solubilization, dispersibility in water and conductivity measurements may be used to determine whether the microemulsion is an (o/w)- or a (w/o)-type. A water-soluble dye will disperse in an (o/w) microemulsion while it will remain in its original form in a (w/o) microemulsion. Likewise, (o/w) microemulsions are generally dispersible in water whereas (w/o) microemulsions are generally not. In addition, (o/w) microemulsions conduct electricity whereas (w/o) do not. The isotropic nature of the system may be confirmed by examination thereof under polarised light. The microemulsions being micellar in nature are isotropic and therefore non-birefringent when examined under polarised light.

From this phase diagram, appropriate percentages may then be read off. The process may then be repeated for other ratios of oil to low HLB surfactant so that an overall picture may be obtained.

Representative pseudo-ternary phase diagram of systems containing a medium-chain oil (CAPTEX 200™) and low HLB surfactant (CAPMUL C8™) in the ratios of 2:1, high HLB surfactant (DSS/PEG 400) in a ratio of 1:1, and water is shown in Figure 2. The mixture of oil plus the low HLB surfactant is indicated as component (1), water as component (2) and the high HLB surfactant as component (3). This system produces a wide range of clear, transparent microemulsions which are shown in the phase diagram as the microemulsion field whose field may be usefully be sub-divided into three fields or regions (A), (B) and (C).

This sub-division is based primarily on differences in conductance, viscosity and dilutability in the presence of excess water. Both the viscosity and conductance increase from regions (A), (B) and (C). In the presence of excess of the dispersed phase (saline or water), microemulsions of regions (A) and (B) are inverted to turbid emulsions (o/w) indicative of their original (w/o) nature. In contrast, microemulsions from region (C) remain clear, characteristic of an oil-in-water isotropic system (microemulsion).

Microemulsions within the scope of the present invention are those falling within regions (A), (B) and (C) of the pseudo-ternary phase diagram.

Accordingly, in a further aspect the present invention provides for stable, self-emulsifying microemulsions as hereinbefore defined in which the relative proportions of the various components lie within regions (A), (B) and (C) of the pseudo-ternary phase diagram in Figure 2.

In general, in the representative system, stable clear, transparent liquid microemulsions are obtained when the oil plus low HLB surfactant is present in the range from about 5% to less than 100% , the high HLB surfactant from about 5% to less than 100% and the aqueous hydrophilic phase, i.e. water or saline is from about 0.1% to less than 50% (w/w) of the microemulsion.

By this process of constructing a representative range of phase diagrams, it has been possible to determine appropriate quantities of the various components which will lead to stable, self-emulsifying microemulsions falling within the present invention.

Suitably, the medium-chain fatty acid propylene glycol and/or polyol ester and the low HLB surfactant together comprise from about 5% to less than 100%, (w/w) of the microemulsion. Preferably, from about 30% to about less than 100%, more preferably from about 60% to less than 95%. The medium-chain fatty acid propylene glycol and/or polyol esters and the low HLB surfactant may be combined and mixed at various ratios. Useful (w/o) microemulsions may be obtained when the ratio of medium-chain fatty acid triglyceride to low HLB surfactant is in the range of about 5:1 to about 1.5:1, preferably about 4:1 to about 2:1. It may be found that as the ratio of medium-chain fatty acid propylene glycol and/or polyol ester to low HLB surfactant is increased towards 5:1, region (C) of the microemulsion existence field becomes increasingly predominant.

Suitably, the high HLB surfactant is present in the range of about 5 to less than 100%, prefeably from about 5% to less than 70%, and more preferably from about 5% to less than 40%. In addition, the high HLB surfactant will be admixed with a polyol in a 10:1 to 1:1 ratio, preferably in a 5:1 to 1:1 ratio, more preferably in a 5:1 to 2:1, and most preferably 1:1 ratio.

Suitably the hydrophilic phase comprises from just greater than 0 to about 50%, preferably from about 0.1 to about 20%, and more preferably from about 0.1% to about 10% (w/w) of the microemulsion.

It will be readily appreciated by the skilled person that, in general, an increase in the relative amount of high HLB surfactant will have to be matched by an increase in the relative amount of hydrophilic phase.

In preferred microemulsions of the present invention, the ratio of medium-chain fatty acid fatty acid propylene glycol and/or polyol ester to low HLB surfactant is preferably between 4:1 and 2:1.

The microemulsions of the present invention are substantially non-opaque, that is they are transparent or opalescent when viewed by optical microscopic means. In their undisturbed state, they are optically isotropic (non-birefringent) when examined under polarized light. They exhibit excellent stability at low and ambient temperatures, without phase separation, clouding or precipitation, even over prolonged periods of time. The formulations may be stored in a stable form at various temperatures, such as at 4°C, ambient temperature, 37°C and at 50°C, preferably at 4°C or ambient temperatures. Peptide-containing microemulsions of the present invention exhibit a similar stability (shelf life) profile to that of the corresponding peptide-free microemulsions. Stable (w/o) microemulsions may be formed when the pH of the aqueous phase varies from a pH of approximately 3 to about 8, a property that can be beneficial for drugs exhibiting higher solubility at low or high pH. The micro-emulsions are of varying viscosity. Microemulsions with a relatively higher amount of a high HLB surfactant, DSS/PEG 400 1:1 tend to be more viscous due to the greater viscosity of this material.

Preferably, the diameter of droplets or particles of the microemulsions of the present invention, measured, for instance, as the number-average diameter by laser light scattering techniques, is less than 150 nm, more preferably less than 100 nm, yet more preferably less than 50 nm and most preferably in the range 5 to 35 nm.

The various phases may optionally contain minor amounts of further ingredients, such as, but not limited to:

i) antioxidants such as n-propyl gallate, butylated hydroxyanisole (BHA) and mixed isomers thereof, d-a-tocopherol and mixed isomers thereof, ascorbic acid, propylparaben, methylparaben and citric acid (monohydrate);

ii) stabilizers, such as hydroxypropyl cellulose;

iii) antimicrobials, such as benozoic acid (sodium salt); and

iv) protease inhibitors such as aprotinin.

The microemulsions of the present invention form spontaneously or substantially spontaneously when their components are brought into contact, that is without the

application of substantial energy supply, for instance in the absence of high shear energy such as imparted by homogenization and/or microfluidization or other mechanical agitation. Accordingly the microemulsions may be readily prepared by the simple process of admixing appropriate quantities, with gentle hand mixing or stirring if necessary to ensure thorough mixing. Preferably, the drug is dissolved in the hydrophilic phase, either directly or by dilution of a stock solution thereof and this may then be added to a pre-mixed combination of the oil and the low HLB surfactant with mixing, followed by the high HLB surfactant or *vice versa*. Alternatively, a drug-free microemulsion may be initially prepared by admixing the oil, the low HLB surfactant, the high HLB surfactant and drug-free hydrophilic phase; to which may then be added further hydrophilic phase in which the drug is dissolved. While higher temperatures (40-60°C) may be needed to solubilize all components during the preparation of the microemulsion, the preferred systems may be formulated at room temperature. Formulation at ambient temperature is particularly advantageous for thermolabile active ingredients such as peptides.

Microemulsions of the present invention are pharmaceutical compositions which comprise a therapeutic agent and are therefore intended for use in therapy, for administration to animals, including man.

Accordingly, in a further aspect, the present invention provides a method of treatment which comprises administering an effective amount of a microemulsion as hereinbefore defined comprising a therapeutic agent to a patient in need thereof. Another aspect of the present invention is the use of a formulation as hereinbefore defined for the controlled or sustained release of a therapeutic agent where so desired to a patient in need thereof.

It will be recognized by one of skill in the art that the amount of drug required for therapeutic effect on administration will, of course, vary with the agent chosen, the nature and severity of the condition and the animal undergoing treatment, and is ultimately at the discretion of the physician. Furthermore, the optimal quantity and spacing of individual dosages of a drug will be determined by the nature and extent of the condition being treated, the form, route and site of administration, the particular patient being treated and that such optima can be determined by conventional techniques. It will also be appreciated that the optimal course of treatment, that is, the number of doses given, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The present invention also provides for the use of a medium-chain fatty acid propylene glycol and/or polyol ester, a low HLB surfactant, a high HLB surfactant, a therapeutic

agent and a hydrophilic phase as hereinbefore defined in the manufacture of a medicament.

Microemulsions of the present invention may be used for oral, topical, rectal, intravaginal or other forms of systemic administration and accordingly will be presented in forms suitable for such. Thus for instance, microemulsions intended for oral administration may be presented in soft gelatin capsules while the viscosity characteristics of some of the microemulsions make them suitable for direct topical application. Compositions suitable for oral or topical administration are especially prefered.

The invention will now be illustrated by, but not limited to, the following descriptions (drug-free microemulsions) and examples (drug-containing microemulsions) and biological examples.

DESCRIPTIONS

Description 1 - Phase Diagrams for Representative Microemulsions

A Pseudo-ternary phase diagrams was constructed for the representative system comprising:

a) medium-chain fatty acid diesters of propylene glycol (oil)	CAPTEX 200
b) low HLB surfactant	CAPMUL C8
c) high HLB surfactant	DSS/PEG 400 (1:1)
d) aqueous phase	water

in which the ratio of the oil to the low HLB surfactant was 2:1.

Alternatively a pseudo-ternary phase diagram for the above noted system can be made wherein the oil to the low HLB surfactant will be 5:1, 4:1 or 3:1.

Other alternative pseudo-ternary phase diagrams may be made for the representative system above at the ratios from 2:1 to 5:1 wherein the high HLB surfactant may be DSS pure or DSS plus 15% sodium benzoate solublized in PEG 400 or another polylol in ratios ranging from 10: 1 to 1:1.

The regions of the phase diagram in which microemulsions according to the present invention exist were determined by titrating a mixture of the oil and low HLB surfactant (in a fixed ratio) against the high HLB surfactant and the aqueous phase, noting points of phase separation, turbidity and transparency. The resultant phase diagram is shown as

figures 2. When examined under polarised light, non-birefringent behaviour was observed.

EXAMPLES

Formulations having the following compositions can be prepared in accordance with the description below or as described herein.

Examples 1-5 describe w/o microemulsions comprising CAPTEX 200 and CAPMUL C8 (ratio 2:1); and dioctyl sodium sulfosuccinate/PEG (ratio 1:1) in an aqueous phase which incorporates GHRP (His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2), MW at about 850 or RGD peptide (cyclo(s,s)-(2-mercapto)benzoyl-(N^a-methyl)-Arg-Gly-Asp-(2-mercapto)-phenylamide, MW of about 650), or calcein. The relative proportions are given in the the following table. The formulation of Example 1 lies, for instance, in region A of a suitably prepared pseudo ternary phase diagram, Example 2 formulation within region C, Example 3 within region C and Examples 4 and 5 within region A.

Example	Drug	Drug conc. mg/g form.	CAPTEX 200 & CAPMUL C8 %(w/w)	Na Dioctyl sulfosuccinate (50%) in PEG 400 %(w/w)	aqueous phase[a] %(w/w)
1	GHRP	3.0	65	30	5[a]
2	GHRP	3.0	10	85	5[a]
3	RGD Peptide	3.0	10	85	5b
4	RGD Peptide	3.0	65	30	5[b]
5	Calcein	0.8	65	30	5[c]

Footnotes to table:

[a] aq. = isotonic soln containing acetic acid and sodium chloride at pH 5.0;

[b] saline.

[c] isotonic 10 mM Tris pH 7.4

Alternatively the aqueous phase can be an isotonic solution at pH ranging from 3 to 8.

These microemulsions were formulated by adding the hydrophilic phase to the solution of dioctyl sodium sulfosuccinate in PEG. To this mixture the oil plus the low HLB surfactant mixture was subsequently added and thoroughly mixed by hand shaking to produce a clear and transparent microemulsion.

Alternatively, the hydrophillic phase can be added to the appropriate amounts by weight of a mixture of the oil and the low HLB surfactant, to which was then added the high HLB surfactant, with gentle stirring (magnetic hot plate).

Active ingredient incorporating microemulsions can be prepared in a similar manner to that shown above, by either dissolving the appropriate amoung of the drug in the appropriate amount of the aqueous phase or preferably, using a stock solution which was then further diluted if so required, and with vortex stirring if necessary to obtain complete disssolution.

BIOLOGICAL EXAMPLES:

Bioavailability of Calcein

Using a standard unconscious rat model (Walker et al, Life Sciences 47, 29-36, 1990), the intraduodenal bioavailability of the model compound calcein (5(6)-carboxyfluorescein, MW=623) when dosed as the microemulsion of Example 5 was assessed and compared with that obtained when the same compound was dosed by the same route but as a solution in isotonic Tris buffer. The levels of the compound in the plasma samples were determined using fluorescence spectroscopy. After i.d. dosing at 1.25 µMol/kg (1.0ml/kg microemulsion), the bioavailability was 26.2 +/- 3.6 %(n=5). In comparison, the bioavailability adminstered as an isotonic Tris buffer as only 1.3 +/- 0.5% (N=5).

Significant plasma levels of calcein were obtained even after 4 hours post dosing with the microemulsion, indicative of a controlled release or sustained release/ absorption. Hence another aspect of the present invention is the use of a microemulsion formulation as herein before defined for use in the controlled release or sustained release of a thereaputic agent where desired.

The bioavailability determination as noted above, is a well recognized experiment to those of skill in the art, but is reiterered herein for convenience as follows:

Male rats which are fasted overnight when employed for the absorption studies. Intravenous (i.v.) or intraduodenal (i.d.) administration of the compound (in this instance Calcein) either from a solution of a microemulsion is carried out using conventional methods.

For the i.v. administration, fasted rats are anesthetized with an intraperitoneal injection of a mixture of Rompun (5mg/kg) and Ketset (35mg/kg) and a jugular catheter is implanted. Rats are allowed to recover from surgery for 1 day. Catherized rats were fasted for 18 hr prior to the administration of the compound. Each compound is administered by lateral tail-vein administration. Blood samples of 0.5ml aliquots were

collected at 0, 1, 3, 5, 15, 30, 45, 60, 90, 120, 150 and 180 minutes. The 0 min sample is taken 15 min prior to administration of the dose. Plasma is removed from whole blood by centrifugation at 1600x g for 5 min, and then stored at -20C in 250µl aliquots per sample. The blood pellet is reconstituted with 12.5 units heparinized saline and returned to the appropriate rat via the jugular catheter. After the experiment, rats are euthanized with i.v. administration of pentobarbital.

For i.d. administration, in addition to jugular catheters, duodenal catheters are surgically implanted in anesthetized rats and the animals allowed to recover from surgery for 4-5 days. The compound is administered either from a solution or microemulsion via the duodenal catheter. Blood samples of 0.5 ml aliquots are collected via jugular catheter in heparinized eppendorf tubes at 0, 10, 30, 60, 120, 180, 240 and 1440 min. The 0 min sample is taken 15 min prior to administration of the dose. Plasma is collected for analysis and the blood returned to rats as described for i.v. administration protocol. The stool of each rat over time is evaluated for consistency by a rank of soft, soft/watery, or mucoid.

Upon termination of the absorption study (4-6, or 24 hrs post-dosing) the animals are euthanized with asphyxiation using carbon dioxide and exanguianated. An abdominal incision is then made and the entire GI tract removed and observed under a microscope at 50x magnification.

Plasma levels of Calcein are determined by fluorescence using a Perkin Elmer LS 50 luminescence spectrometer at excitation and emission wavelenghts of 490 and 515 nm respectively. The bioavailability (%F) is calculated from the AUC (area under the plasma concentration-time curve) following i.d. or i.v. dosing using the following equation:

$$\%F = (AUC_{id}/AUC_{iv}) \times (Dose_{iv}/Dose_{id}) \times 100$$

The formulations of the present invention may be tested for GI irritation assessment with and without an active ingredient by the following method:

Oral Dosing in Rats/GI Irritation Assessment

Suitable rats for use in this assement are male Sprague-Dawley (Caesarian Delivery - Virus Antibody Free; Charles River Laboratories). The rats are fasted overnight the day before the experiment. Dosing with the microemulsion at the desired dose is done by gavage at a volume not exceeding 10 ml/kg. Upon termination of the experiment animals are euthanized with asphyxiation using carbon dioxide and exsanguinated. Abdominal incisions are then performed and gross observations of the gastric and duodenal mucosa are made at naked eyes and under a microscope (Nikon model SMZ-10 binocular microscope).

One aspect of the present invention are the formulations of w/o self-emulsifying microemulsions with or without peptide which produce little, if any, damage along the GI tract upon oral administration. The present formulations may be given orally by gavage

(preferably at three rats per formulation). After 24 hrs the animals are exsanguinated and upon abdominal incisions are examined both by naked eye and under the microscope. The mucosal surface of both the stomach and duodenum of the animals are examined to see if they are free of any lesions at naked eye.

Oral Bioavailability of an RGD Peptide in Rats:

In the procedure described below microemulsions formulated as described above and containing, for instance, 3mg of peptide per gr of microemulsion are tested in the following manner for oral bioavailability.

a) Intravenous (iv) administration of peptide in saline

Fasted rats are given an intraperitoneal (i.p.) injection and surgically fitted with femoral artery catheters. Rats ware allowed to recover from the surgery for 1 day. Catherized rats are fasted for 18 hr prior to the experiment. Each rat receives 3mg of peptide by lateral tail-vein administration from a solution prepared as follows:

10.84 mg peptide q.s. to 8ml with 0.9% saline solution. Blood samples of 0.5ml aliquots are collected at 0, 1, 3, 5, 10, 15, 30, 45, 60, 90, 120, 150 and 180 minutes. The 0 min. sample is taken 15 min prior to administration of the dose. Plasma is removed from the whole blood by centrifugation at 16000Xg for 5 min, and then plasma is stored at -20°C in 250µl aliquots per sample. The blood pellet is reconstituted with heparinized saline and returned to the appropriate rat via catheter. After the experiment, rats are euthanized with iv administration of pentobarbital.

b) Intraduodenal (i.d.) administration of peptide in microemulsion

Fasted rats are given an i.p. injection of anesthesia cocktail and surgically fitted with jugular and duodenal catheters. Rats are allowed to recover from the surgery for 4-5 days. Catherized rats are fasted 18-20 hrs. prior to the experiment. Each rat receives 10mg of peptide in either microemulsion or saline solution. Blood samples of 0.5ml aliquots are collected via jugular catheter in heparinized eppendorf tubes at 0, 10, 30, 60, 120, 180, 240 and 1440 minutes. The 0 min sample is taken 15 min prior to administration of the dose by duodenal catheter. Plasma is collected for analysis and the blood returned to rats as described in the i.v. administration (part a) above. After 1440 min, rats are euthanized by iv administration of pentobarbital, exsanguinated and the GI tract removed for gross observation.

c) Analysis of peptide plasma concentration

Standards are placed before and after the sample for HPLC analysis. A 50µl aliquot for 0-200 ng peptide, 25µl aliquot for 1000-2000 ng peptide, 15µl aliquot for 10,000 ng peptide and a 50µl aliquot of each sample is analyzed by post-column fluorescence detection. Fluorescence chromatography data is collected and integrated using a Nelson Chromatography Data System. The peak area ration (Y) and peptide standard concentration (X) are used to determine the slop of a line which is forced through the origin from the equation: slope = (sum of X*Y)/(Sum of X^2). The slope represents the relationship between peak area ratio and peptide plasma concentration for the samples.

d) Calculation of Bioavailability

First, the area under the plasma concentration curve (AUC) from 0 to 240 minutes is determined for each rat. For id administration, percentage bioavailability is determined for each animal by the following equation with the average AUC from iv administration: $[(AUC_{id}/AUC_{iv})*(dose_{iv}/dose_{id})] * [100]$.

The oral bioavailability data for the RGD peptide in rats after intraduodenal administration of a microemulsion containing the above formulations incorporating a fibrinogen receptor antagonist of a peptide dose may then be obtained in the above noted manner.

When applicable, the formulations of the present invention are tested for *in vivo* activity. As one of the active ingredients utilized herein is a fibrinogen receptor antagonist a platelet aggregation assay is employed to determine pharmacological activity of the peptide from microemulsions. These studies are carried out as shown below.

Oral Dosing in Dogs/Platelet Aggregation Assay :

Dogs used in this assay are male Mongrels (i.e. from mixed breeds). The dog(s) are fasted overnight the day before the experiment. The cephalic vein of choice is prepared for the indwelling catheter in the following way: the area is first shaved and cleaned with a gauze soaked in 70% alcohol. An indwelling catheter is placed in the caphalic vein and attached to a luer lock adapter filled with 3.8% sodium citrate. The catheter is securely taped down. When a blood sample is withdrawn, a 0.3 ml of blood is withdrawn into a separate 1 cc syringe before the actual sample so that dilution of the blood sample from the sodium citrate contained in the luer lock adapter is avoided. Then 2.7 ml of blood are drawn in a 3 cc syringe and placed in a Venoject vacuum tube containing 0.3 ml of 3.8% sodium citrate and labelled with the appropriate time point.

The tube containing the blood sample in 3.8% sodium citrate is gently inverted few times to mix components and then 1 ml is withdrawn for the whole blood aggregation assay. The rest of the blood sample is transferred to an eppendroff tube and upon centrifugation the supernatant plasma is removed and transferred to a new tube which is then frozen for subsequent HPLC analysis to determine peptide content.

Just after the zero time point blood sample is withdrawn, an appropriate dose of microemulsion with or without peptide is administered orally to the dog using a size 12 gelatin capsule.

The blood samples are then assayed for platelet aggregation inhibition using the Chromo-Log whole blood aggregometer. The instrument is warmed to 37°C before samples are run and the probe is cleaned with distilled water and a soft brush. The probe is attached to the aggregometer and placed in a cuvette of saline solution and warmed in a side cuvette well in the aggregometer. For the actual assay, 1 ml of the 2.7 ml of blood sample mixed with the 0.3 ml 3.8% sodium citrate contained in the Venoject vacuum tube is added to a cuvette and placed in the aggregometer well. A stir bar is placed in the cuvette and set at 900 rpm. The probe is placed firmly into the test cuvette and the lid is shut. Baselines, zero and calibration are set. Calibration is set equal to 20 = 5 ohms. The stirring cuvette is permitted to settle for five minutes at which point 5 µl of collagen is added to the whole blood that is being stirred to yield to a 5 µg/ml final solution in the cuvette.

The reaction is monitored for two minutes once the slope change reaches the baseline of the collagen addition, calculating the change in ohms per minute using the slope of the two minutes. The change in ohms per minute is calculated as a % of the control. The control value is determined by the average of the -15 and the 0 time points. After each use the probe is removed and cleaned with distilled water and wiped with a soft cloth and brush.

Discussion and Conclusion:

A dog is considered a good model to assess the pharmacological effect of one class of peptides of interest herein, the RGD containing fibrinogen receptor antagonists. Experiments are conducted as described above, with a peptide dose of 3 mg/kg or microemulsion dose of 0.5 ml/kg. Control experiments where the peptide is given orally in a saline solution are independently carried out earlier and serve as a useful comparison to the effects seen with the microemulsion-formulated peptide.

As one of the active ingredients utilized herein is a Growth Hormone Releasing Peptide the appropriate assay for in vivo activity is determined as shown below.

In Vivo Testing of GHRP-Containing Microemulsion:

A microemulsion with a composition (w/w) in accordance with the Examples above is made. Upon preparation, they are further stored in a stable form at ambient temperature for approximately 48 hrs before the in vivo evaluation. A control solution of a GHRP peptide, His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2, in saline at 1.5 mg/ml is also prepared.

Dosing is done by single intraduodenal administration of GHRP at 3 mg/kg in male rats in saline solution (control) and in the aforementioned microemulsion using 3 rats in each case. Prior to actual sampling and dosing, each rat is anesthetized with Pentobarbitol at 50 mg/kg i.p, diluted with saline to a final volume of 1 ml. The rats stay anesthetized for the entire experiment. Dosing is achieved in the following way: a small incision 2-3 cm long is made on the abdominal midline, and then a purse-string suture is placed on the duodenal muscle. A small hole is made in the center of the purse-string suture in which a blunt 23 G stub needle attached to a tuberculin syringe is inserted to deliver the dose. Upon completion of dosing, the purse-string is tied to close the opening. The incision is closed with wound clips. A 0.2 ml blood sample is obtained via jugular catheter at the following intervals: -15, 0, 5, 10, 15, 30, 45, 60, 90, and 120 minutes. Blood samples are stored on ice and subsequently analyzed for Growth Hormone by an RIA method.

Analysis of the samples generated from the experiment mentioned above need to have determined the pharmacological activity of GHRP. Positive data will indicate that Growth Hormone Releasing Peptide is orally active from the microemulsion formulation of the present invention. However, blood levels and actual bioavailability need to be correlated to observed pharmacological activity.

The amount of active ingredient required for therapeutic systemic administration will, of course, vary with the compound chosen, the nature and severity of the condition, and the mammal, including humans, undergoing treatment, and is ultimately at the discretion of the physician.

Ultimately, the present invention also includes a method of treatment which comprises administering an effective amount of a pharmaceutical composition as defined herein to a patient in need thereof. Preferably, the therapeutic agent is selected from a fibrinogen receptor antagonist peptide, a Growth Hormone Releasing Peptide, a vasopressin, elcatonin, a calcitonin, a calcitonin-gene releated peptide, a porcine somatostatin, insulin or a homolog or analog thereof. The disease states and uses of each of the aforementioned thereapeutic agents is well known to those skilled in the art

and for a number of the agents alerady cross referenced to their respective patents. For instance, use as platelet aggregation inhibitors, growth promoters, for the treatment of osteoporosis, and diabetes.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A pharmaceutically acceptable, stable, self-emulsifying water-in-oil (w/o) or oil in water (o/w) microemulsion comprising:

a) a lipophilic phase comprising medium-chain fatty acid propylene glycol esters or medium-chain fatty acid polyol esters, or mixtures thereof and a low HLB surfactant and in which the ratio of the medium-chain fatty acid propylene glycol ester or medium-chain fatty acid polyol esters, or mixtures thereof to the low HLB surfactant is from 5:1 to 1.5:1;

(b) an admixture of a polyol and at least one high HLB surfactant which is

i) a sulfate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfate, an aryl sulfate, an aliphatic-aryl sulfate, or mixtures thereof;

ii) a sulfonate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfonate, or aryl sulfonate, an aliphatic-aryl sulfonate, or mixtures thereof;

iii) a sulfosuccinate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfosuccinate, an aryl sulfosuccinate, an aliphatic-aryl sulfosuccinate, or mixtures thereof; or

iv) a mixture of any of i), and/or ii), and/or iii) above;

(c) an aqueous hydrophilic phase; and

(d) a water-soluble therapeutic agent.

2. The microemulsion according to claim 1 in which the medium-chain fatty acid propylene glycol and/or polyol esters comprises from 50 to 100% (w/w) of caprylic acid and from 0 to 50% (w/w) of capric acid ester.

3. The microemulsion according to claim 2 in which the medium-chain fatty acid propylene glycol and/or polyol esters is formed essentially from caprylic acid.

4. The microemulsion according to claim 1 or 2 in which the low HLB surfactant is a medium-chain fatty acid monoglyceride or diglyceride or a mixture thereof, optionally comprising a small amount by weight of free medium-chain fatty acid.

5. The microemulsion according to claim 4 in which the medium-chain fatty acid monoglyceride or diglyceride is formed from 50 to 100% caprylic acid and from 0 to 50% capric acid.

6. The microemulsion according to claim 5 in which the medium-chain fatty acid monoglyceride or diglyceride is formed essentially from caprylic acid.

7. The microemulsion according any of claims 1, 2 or 4 in which the high HLB surfactant is selected from the group consisting of polyoxyethylene fatty acid esters, polyoxyetheylene-sorbitan fatty acid esters, polyethylene glycol long-chain alkyl ethers and polyethylene glycol long-chain alkyl esters.

8. The microemulsion according to claim 7 in which the high HLB surfactant is a pharmaceutically acceptable water-soluble salt, an alkali metal salt, an ammonium or a quaternary ammonium salt, or a primary or secondary amine.

9. The microemulstion according to claim 1 in which the high HLB surfactant is a medium-chain alkyl or di-alkyl sulfate, or sulfonate, or sulfosuccinate.

10. The microemulsion according to claim 9 wherein the high HLB surfactant is a salt of dioctylsulfosuccinate or dodecyl sulfate.

11. The microemulsion according to any of claims 7 to 10 in which the polyol is glycerol, or polyethylene glycol.

12. The microemulsion according to claim 1 wherein the polyol is polyethylene glycol and the polyol is admixed in a 10:1 to 1:1 ratio with the high HLB surfactant.

13. The microemulsion according to claim 1 wherein the medium chain fatty acid propylene glycol esters are mixtures of caprylic and capric diesters.

14. The microemulsion according to claim 1 in which the therapeutic agent is a peptide.

15. The microemulsion according to claim 14 in which the peptide has a molecular weight in the range 100 to 10,000 or contains from 2 to 35 amino acid moieties.

16. The microemulsion according to claim 15 in which the peptide is a fibrinogen receptor antagonist peptide (an RGD peptide), a vasopressin, a calcitonin or an insulin.

17. The microemulsion according to claim 1 in which the diameter of droplets or particles is less than 150 nm.

18. The microemulsion according to claim 1 adapted for oral delivery or topical application.

19. The microemulsion according to claim 1 which further provides for a sustained release absorption of the therapeutic agent in a mammal.

20. The microemulsion according to claim 1 which further provides for oral bioavailability enhancement of the therapeutic agent in a mammal.

21. A self-emulsifying (w/o) or (o/w) microemulsion optionally comprising a water soluble therapeutic agent in which the relative proportions of the following components:
(1) a lipophilic phase comnprises medium-chain fatty acid propylene glycol or medium-chain fatty acid polyol esters, or mixtures thereof, and a low HLB surfactant and in which the ratio of the medium-chain fatty acid propylene glycol ester or medium-chain fatty acid polyol esters, or mxtures thereof, to the low HLB surfactant is from 5:1 to 1.5:1;
(2) an admixture of at least one high HLB surfactant which is a medium chain alkyl or dialkyl sulfate, medium chain alkyl or dialkyl sulfonates, or medium chain alkyl or dialkyl sulfosuccinate with a polyol; and
(3) an aqueous phase; such that the resulting composition lies within any one of the regions (A), (B) and (C) of Figure 2.

22. A process for preparing a microemulsion as defined in claim 1 which process comprises admixing appropriate amounts of the ingredients thereof in order that is convenient.

23. A pharmaceutically acceptable stable, self-emulsifying water-in-oil (w/o) or oil in water (o/w) microemulsion comprising: a) a lipophilic phase having a medium-chain fatty acid fatty acid propylene glycol and/or polyol esters and a low HLB surfactant and in which the ratio of the medium-chain fatty acid fatty acid propylene glycol and/or polyol esters to the low HLB surfactant is from 5:1 to 1.5:1;
(b) an admixture of a polyol and at least one high HLB surfactant which is (i) a sulfate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfate, an aryl sulfate, an aliphatic-aryl sulfate, or mixtures thereof; (ii) a sulfonate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfonate, or aryl sulfonate, an aliphatic-aryl sulfonate, or mixtures thereof; (iii) a sulfosuccinate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfosuccinate, an aryl sulfosuccinate, an aliphatic-aryl sulfosuccinate, or mixtures thereof; or (iv) a mixture of any of i), and/or ii), and/or iii) above;
(c) an aqueous hydrophilic phase.

$$\left| \frac{\text{Oil}}{\text{Low HLB Surfactant}} \right| = x \text{ (fixed)}$$

(1)

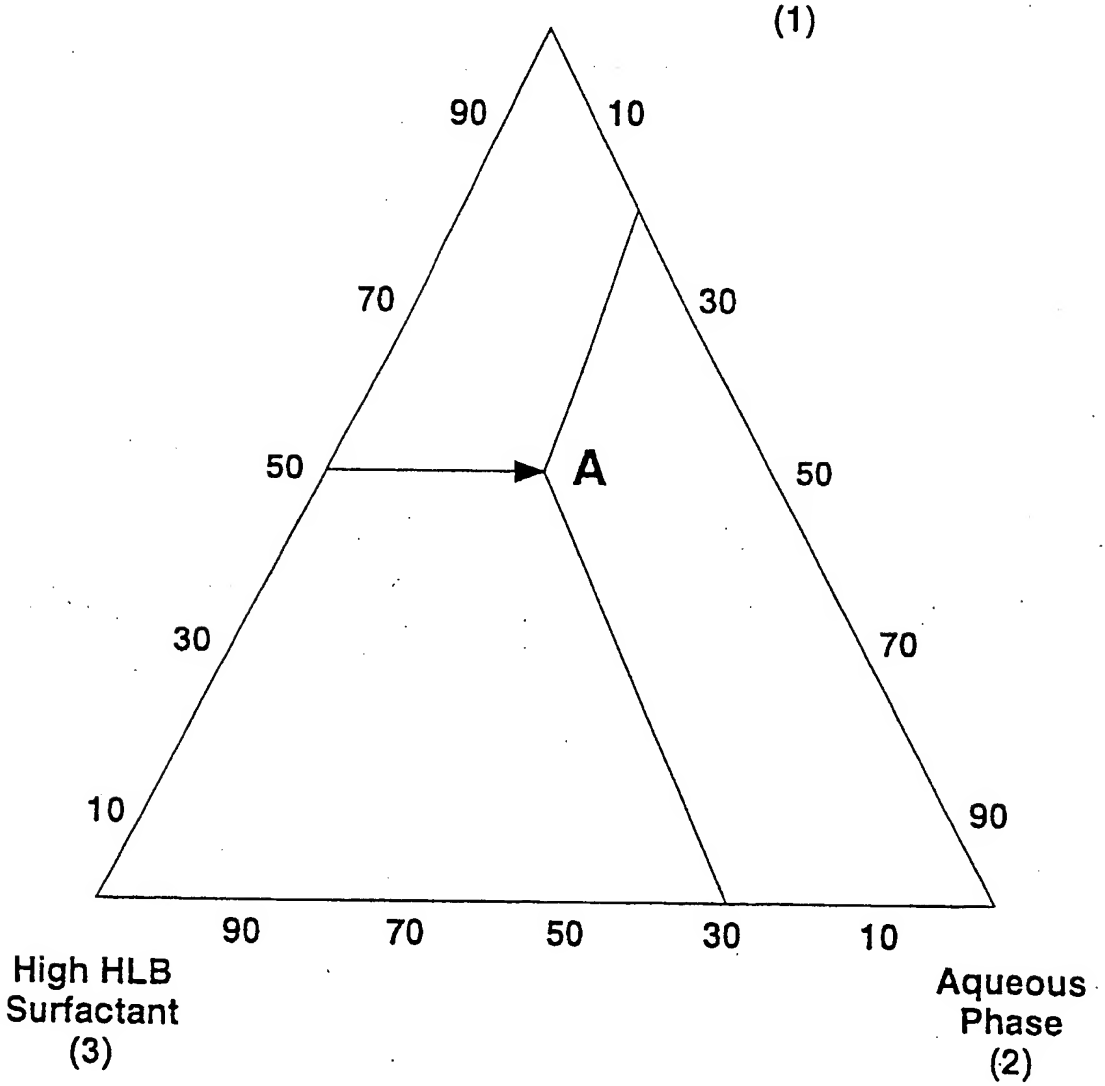

Figure 1

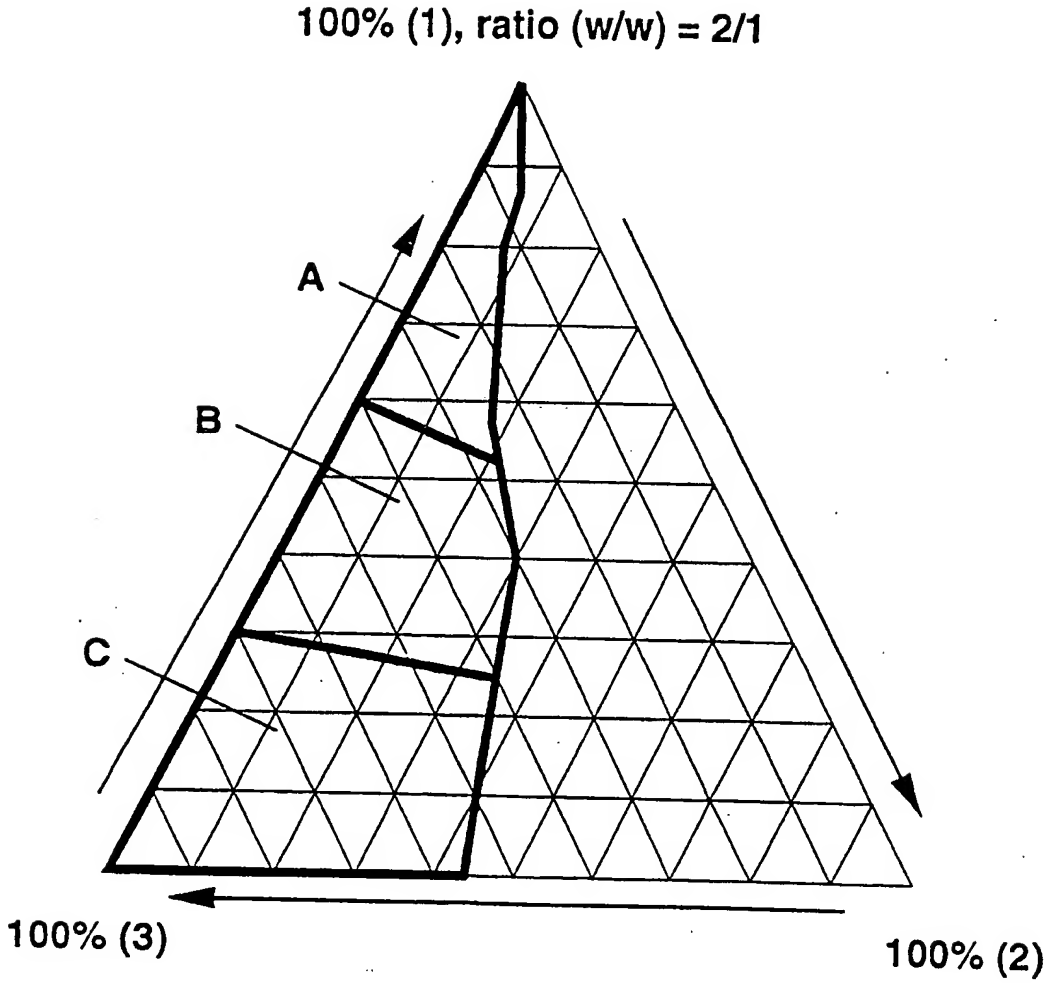

Figure 2

INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/US94/02062

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 37/02
US CL : 514/2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS CAS Online, Dialog

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,110,606 (GEYER et al.) 05 May 1992, see entire document.	1-24
A	Science, Volume 240, Kahlweit, issued 29 April 1988, "Microemulsions" pages 617-621, see entire document.	1-24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
17 MAY 1994	24 MAY 1994

Name and mailing address of the ISA/US	Authorized officer
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